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Brill-Zinsser Disease in North America

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THE ILLNESS NOW KNOWN as recrudescent typhus or Brill-Zinsser disease probably has been known to physicians for more than 80 years. In 1898 Brill described the cases of 17 patients with an illness resembling typhoid fever, with the exception that all had a negative Widal reaction. By 1910 Brill[1] had collected and reported on 221 cases of this clinical syndrome, most of which occurred in European immigants. In 1934 Zinsser reported 538 cases of Brill* disease which he had collected over some 30 years; 95 percent of these patients were immigrants from eastern and southeastern Europe who had lived in areas where typhus had occurred in epidemic form. Zinsser[2] suggested that Brill disease represented a recrudescence of epidemic typhus originally acquired in Europe. In 1950 Murray and co-workers[3] reported 14 cases of Brill disease and showed by clinical and serological data that the cause was *Rickettsia prowazeki,* the same agent responsible for epidemic typhus. These authors concluded that the clinical diagnosis could and should be made when a fever of unknown origin occurs in a foreign-born person who lived in an area where typhus occurs in epidemic form; when intense, persistent headache occurs, and when a macular and maculopapular rash develops on the fourth to sixth day of illness. There was final proof of the causative agent in 1954 when Price[4] isolated viable *R prowazeki* from abdominal lymph nodes removed from two patients who had immigrated from Russia 20 years earlier and who apparently had had typhus before coming to the United States. Recrudescent typhus is undoubtedly still with us, but has rarely been reported in the 1970's. Our case appears to be the second report of this disease in North America in more than a decade, the other case having been reported in Canada.[5]

*THE WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

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Report of a Case

A 54-year-old man, a machinist, was admitted to Mercy San Juan Hospital in Carmichael, California, on July 1, 1974. Symptoms of illness had developed on June 11, which included headaches, sore throat, fever and enlarged cervical lymph nodes. Three days later he was afebrile, but after six days he began to complain of right upper quadrant abdominal pain; a physical examination at that time disclosed no abnormalities. When examined again on June 30, the patient complained of having severe, steady headaches, temperatures to 38.4°C (101°F) daily for the previous six days and right lower quadrant abdominal pain. His medical history disclosed that he had had epidemic typhus infection in a German concentration camp in Poland in 1944.

On examination at admission the patient, who was found to be heavy-set, had a blood pressure of 160/100 mm of mercury, temperature of 39.6°C (103.4°F) and a heart rate of 86 beats per minute. There were two enlarged nontender cervical lymph nodes, both less than 5 mm in diameter. The neck was supple, the abdomen was soft and nontender, and the skin was hot and dry. There was no rash at the time of admission. There was no hepatomegaly or splenomegaly.

Serial blood counts disclosed a continuously normal leukocyte count with a slight left shift and some toxic granulation of the neutrophils. Results of analysis of urine and urine culture were normal. Six blood cultures failed to yield growth. Lactic dehydrogenase (LDH) determinations were slightly elevated with no specific pattern on isoenzyme testing. On admission serum aspartate aminotransferase (formerly serum glutamic oxaloacetic transaminase [SGOT]) levels were normal at 26 with subsequent rise to 60 units (normal 0 to 50 units). Skin tests for coccidioidomycosis, histoplasmosis, tuberculosis and mumps all yielded negative results. No bacterial pathogens were isolated from specimens from the throat or the feces. Results of examination of cerebrospinal fluid were normal. A screening test for infectious mononucleosis was negative. The titer for antistreptolysin was less than 166 Todd units. Findings on roentgenograms of the abdomen, skull and chest, intra-

venous pyelogram, upper gastrointestinal series, small bowel series and a barium enema study were all normal. Nucleide brain scan and an electrocardiogram showed no abnormalities.

The patient's clinical course was notable for the presence of a continuously severe headache, temperatures ranging between 37.8°C (100°F) and 39.5°C (103°F), myalgia and weakness. On the sixth hospital day, a macular rash appeared transiently on the abdomen, back and arms, returning the following day in a general distribution, but was not visible thereafter. After diagnostic studies were completed, a regimen of 250 mg of tetracycline given orally four times a day was initiated on the eighth hospital day, with defervescence within 48 hours. Headache ceased 24 hours after institution of antibiotic therapy. Strength and the ability to walk returned and the patient was discharged on the tenth hospital day.

TABLE 1.—*Results of Initial Serological Tests*

Antigen	Technique	Dates of Serum Samples 7/9/74	8/14/74	2/28/74
Rocky Mountain spoted fever	CF*	1:8	1:8	ND
Typhus group	CF*	1:512	1:512	1:64
Epidemic typhus	CF†	1:512	1:512	ND
Murine typhus	CF†	1:256	1:256	ND
Epidemic typhus	IFA†	1:8,192	1:2,048	1:512
Murine typhus	IFA†	1:2,048	1:256	1:128

CF = complement fixation; IFA = indirect fluorescent antibody; ND = not done

*Done at the Viral and Rickettsial Disease Laboratory of the State of California Department of Health.
†Done at the Leprosy and Rickettsia Branch of the Virology Division of the Bureau of Laboratories, Center for Disease Control, Atlanta.

TABLE 2.—*Results of Special Indirect Fluorescent Antibody Tests on Serum Sample of 7/9/74**

Antigen	Absorption With Yolk Sac	Murine Typhus	Epidemic Typhus	*Rickettsia canada*
Murine typhus	1:1,024	1:64	1:16	1:1,024
Epidemic typhus	1:16,384	1:4,096	1:16	1:8,192
Rickettsia canada	1:1,024	1:16	1:16	1:16

*Done at the Leprosy and Rickettsia Branch of the Virology Division of the Bureau of Laboratories, Center for Disease Control, Atlanta.

Discussion

This patient's symptoms and signs—high fever, intense and unrelenting headache, a transient macular rash on the trunk during the height of the illness and prompt response to tetracycline therapy—are all typical of Brill-Zinsser disease. On the other hand, the patient's history of an illness characterized by pharyngitis and intermittent low-grade fever for approximately three weeks before the development of the classic features of recrudescent typhus are not characteristic of that disease, as the latter generally has a short, three- to four-day prodromal period.[3] It is doubtful, then, that the patient's earlier symptoms were those of recrudescent typhus but more likely were representative of some nonrickettsial process. The diagnosis in this case was substantiated by the antibody test results (Tables 1 and 2). Complement fixation titers to the typhus group antigen were elevated significantly in the late acute phase of the patient's illness as well as five weeks later, with an eightfold fall occurring several months later, indicating either epidemic typhus or murine typhus. The first two serological studies showed significant elevations to *both* the specific epidemic typhus and the related murine typhus antigens. Indirect fluorescent (IFA) titers on the three serum samples showed somewhat higher titers to the epidemic typhus than to the murine typhus antigen (Table 1). IFA tests carried out on the first serum sample after differential absorption with yolk sac, as a control, as well as the nonpathogenic *Rickettsia canada* and epidemic typhus and murine typhus antigens (Table 2) confirmed that the antibody was specific for epidemic typhus. It was completely absorbed with epidemic typhus antigen but not with the murine typhus antigen or *Rickettsia canada*. Furthermore, the antibody was found to be almost all IgG, the characteristic response in Brill-Zinsser disease, in contrast to primary epidemic typhus and murine typhus in which IgM antibody predominates early in the disease.

This case illustrates that Brill-Zinsser disease can appear some 30 years after the initial bout of louse-borne typhus, due to the fascinating ability of the responsible microorganism, *R prowazeki,* to remain dormant in the reticuloendothelial system for many years. The reasons for recrudescence have never been elucidated.

In contrast to cases of classic louse-borne typhus, recrudescent typhus carries a low mortality, and the untreated disease is shorter in duration than classic typhus. Nevertheless, it is clear that patients with Brill-Zinsser disease, such as our patient, can remain in a toxic condition and be ill for many days; also, fatalities have been described.[1,3] The severe, unrelenting headache generally persists throughout the 10- to 14-day

febrile course and its response to symptomatic therapy is usually poor. The rash typically begins on the fourth to sixth day of the illness and consists of small, discrete macules of 1 to 10 mm which are generally noted first on the chest or abdomen, but which can be present later on the extremities. The rash may be transient, as in our patient, or persist for a few days. The response to the tetracycline group of antibiotic drugs is excellent, as in epidemic typhus, and it has been noted recently that even one dose of doxycycline can lead to prompt defervescence.[6] Therefore, therapy with a tetracycline drug should be initiated when classic features are present.

In contrast to epidemic typhus, Brill-Zinsser disease is not generally associated with a positive Weil-Felix test; for example, in our patient, the *Proteus* OX19 titer was only 1:20. The complement fixation test generally attains a maximum level by the 10th to 11th day of illness in contrast to epidemic typhus in which the maximum titers are not usually achieved until two weeks after onset. Therefore, in suspected cases it is important to obtain serum samples during the acute phase of illness for antibody testing to demonstrate a later rise in titer.

It was postulated by Murray and co-workers in 1950 that large numbers of cases of Brill-Zinsser disease might be found in this country due to the large influx of immigrants who had experienced typhus in Nazi concentration camps and elsewhere during World War II.[3] However, very few cases have been reported in North America in the 1960's and 1970's; the last case was reported in Canada in 1974.[5] Possibly, the rarity of recent reports of this disease is due partially to unfamiliarity with its manifestations and the lack, therefore, of attempts to make a specific diagnosis. We hope that this case report will stimulate continued attempts to diagnose Brill-Zinsser disease in the future.

Summary

A case of recrudescent typhus occurring 30 years after the initial bout of epidemic typhus is described. This disease should continue to be considered in the differential diagnosis of fever of undetermined origin in immigrants, particularly those from eastern Europe, from regions where typhus infection may have occurred in the past. The clinical diagnosis should be confirmed by appropriate serological tests.

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Choledochocele Associated With Acute Hemorrhagic Pancreatitis

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CHOLEDOCHAL CYSTS have been reported more than 1,000 times in the medical literature since the first one was described by Douglas in 1852.[1-4] However, the incidence of choledochoceles or type III choledochal cysts as classified by Alonso-Lej[5] is rare, and only 21 cases have been reported.[3,4,6-21] A patient with this type of lesion, which was associated with hemorrhagic pancreatitis and necrosis of the head of the pancreas, was recently treated by us and that case is the basis for this report.

Report of a Case

A 40-year-old man was admitted to Providence Hospital in Anchorage, Alaska, on June 7, 1978, after the sudden occurrence of severe epigastric pain and a temperature that rose to 39°C (102.2°F). The level of serum amylase was 2,700 units (normal less than 200). Past medical history included multiple episodes of abdominal pain.

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